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ORIGINAL RESEARCH

Impact of Antithrombotic Regimen on Mortality, Ischemic, and Bleeding Outcomes after Transcatheter Aortic Valve Replacement

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ABSTRACT

Introduction: Optimal antithrombotic therapy after transcatheter aortic valve replacement (TAVR) remains unclear. We evaluated the association between antithrombotic regimens and outcomes in TAVR patients.

Methods: We retrospectively analyzed consecutive patients who underwent TAVR at a single academic center from April 2009 to March

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2014. Antithrombotic regimens were classified as single or dual antiplatelet therapy (AP), single antiplatelet plus anticoagulant (SAC), or triple therapy (TT). The primary endpoint was a composite of death, myocardial infarction (MI), stroke, and major bleeding. Adjusted hazard ratios (HRs) were obtained with best subset variable selection methods using bootstrap resampling.

Results: Of 246 patients who underwent TAVR, 241 were eligible for analysis with 133, 88, and 20 patients in the AP, SAC, and TT groups, respectively. During a median 2.1-year follow-up, 53.5% had at least one endpoint—the most common was death (68%), followed by major bleeding (23%), stroke (6%), and MI (3%). At 2 years, the composite outcome occurred in 70% of TT, 42% of SAC, and 31% of AP patients. Compared to AP, adjusted HRs for the composite outcome were 2.88 [95% Confidence intervals (CI) (1.61–5.16); $p = 0.0004$] and 1.66 (95% CI [1.13–2.42]; $p = 0.009$) in the TT and SAC groups, respectively. Mortality rates at 2 years were 61% in the TT, 32% in the SAC, and 26% in the AP groups ($p = 0.005$).

Conclusions: The risk of the composite outcome of death, MI, stroke, or major bleeding at 2-year follow-up was significantly higher in TAVR patients treated with TT or SAC versus AP, even after multivariate adjustment.

Keywords: Antithrombosis; Aortic stenosis; Transcatheter aortic valve replacement

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has become an established treatment for patients with symptomatic, severe aortic stenosis with intermediate, high, or prohibitive surgical risk [1–5]. Despite advances in patient selection, operator experience, and valve delivery systems, ischemic and bleeding complications remain important concerns after TAVR, as they are associated with increased morbidity and mortality [6–8]. However, limited data are available comparing long-term outcomes with varying antithrombotic regimens after TAVR.

Current guidelines recommend dual antiplatelet therapy with aspirin (indefinitely) and clopidogrel (for 1–6 months) after TAVR in patients with no indication for therapeutic oral anticoagulation (OAC). In patients with an indication for OAC, guidelines generally recommend against the use of triple therapy [9–12]. However, these recommendations have been made empirically and vary amongst professional societies, leading to heterogeneity in clinical practice [13].

We sought to examine the association between different antithrombotic regimens and the risk of mortality, ischemic, and bleeding outcomes in a non-selected clinical population undergoing TAVR. Specifically, we compared outcomes among TAVR patients prescribed single or dual antiplatelet therapy (AP), a single antiplatelet agent plus OAC (SAC), or triple therapy (TT) with dual antiplatelet therapy (DAPT) and OAC.

METHODS

Study Population

We retrospectively analyzed consecutive patients who underwent TAVR at Brigham and Women's Hospital in Boston, Massachusetts, from April 2009 through March 2014. Baseline medical history, routine laboratory testing, electrocardiography, echocardiography, CHA2DS2-VASc score, ATRIA score, New York Heart Association functional classification, pre-procedure antithrombotic regimen, and TAVR

procedural characteristics were collected. Patients were then prospectively followed for ascertainment of study outcomes. The Institutional Review Board of Partners Healthcare in Boston, Massachusetts, approved the study, and signed informed consent was obtained from each patient. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Antithrombotic Regimen

The antithrombotic regimen was noted pre-TAVR, at the time of discharge from TAVR admission, at 30 days, at 1 year, and through April 2016 using electronic health records and telephone follow-up. Antithrombotic regimens were classified as single or dual antiplatelet therapy only (AP), single antiplatelet plus anticoagulant therapy (SAC), or triple therapy (TT) with DAPT plus OAC. Patients were grouped according to the antithrombotic regimen at the time of latest follow-up for the purposes of the statistical analysis.

Outcomes

The primary endpoint was the composite of death, myocardial infarction (MI), stroke, or major bleeding (requiring hospitalization, life-threatening, or fatal). Outcomes were assessed according to Valve Academic Research Consortium-2 definitions [14] at discharge, 30 days, 1 year, and through April 2016 using electronic medical record data and telephone follow-up with a standardized questionnaire.

Statistical Analysis

To determine associations between antithrombotic therapy group and the primary composite outcome, a Cox proportional hazards model was used. A multivariable model was developed with best subset variable selection methods using bootstrap resampling in order to account for model variation due to small sample size [15]. The final model included adjustment for

chronic lung disease, prior percutaneous coronary intervention (PCI), male sex, age, and low-gradient aortic stenosis (defined as left ventricular ejection fraction < 50%, aortic valve area < 1.0 cm², and mean aortic valve gradient < 40 mmHg). Results are reported as adjusted hazard ratios (HR) and 95% confidence intervals (CI). Proportional hazards assumption for the final model was assessed by score tests using scaled Schoenfeld residuals. Crude cumulative event rates were calculated by the complement of Kaplan–Meier survival estimates, and log-rank test *p* values are also reported. All reported *p* values are two-sided, and significance level was set at alpha 0.05. Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 outlines the baseline characteristics of each study group. A total of 246 patients underwent TAVR from April 2009 to March 2014. Of these, five patients were excluded for the following reasons: prescribed no antithrombotic therapy (*n* = 2) and incomplete post-discharge follow-up (*n* = 3), leaving 241 patients for final analysis. The baseline characteristics among the AP (*n* = 133), SAC (*n* = 88), and TT (*n* = 20) groups were similar, with the exception of rates of atrial fibrillation or flutter (*p* < 0.01), indication for OAC (*p* < 0.01), aortic valve mean gradient (*p* = 0.044), and aortic valve peak velocity (*p* = 0.047) (Table 1). Overall, 67.2% of cases were done with a transfemoral approach, while 16.2% and 15.8% of cases were performed via a transapical and transaortic approach, respectively.

Of the 241 patients followed for a median of 2.1 years (interquartile range, 0.7–2.9 years), 53.5% (*n* = 129) had at least one endpoint. The components of the composite outcome in the cohort were distributed as death (68%), major bleeding (23%), stroke (6%), and MI (3%) at 2-year follow-up. The risk of the composite outcome was highest with TT (70%; HR 2.88, 95% CI 1.61–5.16, *p* = 0.0004) and intermediate with SAC (42%; HR 1.66, 95% CI 1.13–2.42, *p* = 0.009), compared to AP (31%) at 2 years

(Fig. 1). Mortality rates at 2 years were 61%, 32%, and 26% (*p* = 0.005) in the TT, SAC, and AP groups, respectively, while major bleeding rates were 29%, 18%, and 9.1%, respectively (*p* = 0.02). Rates of stroke and MI were low and similar among groups.

A total of 132 patients in the cohort had an indication for OAC (88.6% had atrial fibrillation or flutter), including 40 in the AP group, 76 in the SAC group, and 16 in the TT group. Among patients with an indication for OAC, the composite outcome occurred in 69% of TT, 38% of SAC, and 38% of AP patients (*p* = 0.06) at 2-year follow-up.

DISCUSSION

This study evaluated the association between post-TAVR antithrombotic regimen and the composite outcome of death, MI, stroke, or major bleeding in a single-center cohort of 241 consecutive patients with at least 2-year follow-up. Patients treated with TT or SAC versus AP had a higher incidence of the composite outcome, even after multivariate adjustment. This finding was driven by an increase in both mortality and major bleeding in the TT and SAC groups.

TAVR patients are at high risk for both ischemic and bleeding events by virtue of comorbidities and the procedure itself. Both types of complications are associated with increased morbidity and mortality. Moreover, TAVR patients frequently undergo pre-emptive coronary artery stenting, which necessitates DAPT, and approximately half have atrial fibrillation requiring OAC. Given this complex interplay, identifying an antithrombotic regimen that achieves an optimal balance between ischemic protection and bleeding risk mitigation is paramount in this patient population. Nevertheless, guideline recommendations for antithrombotic therapy after TAVR remain empiric, and are extrapolated from the PCI experience and early TAVR clinical trial protocols [16].

Our analysis indicates that treatment with TT or SAC is associated with adverse clinical outcomes compared to treatment with AP alone

Table 1 Patient characteristics by study group

	AP (<i>n</i> = 133)	SAC (<i>n</i> = 88)	TT (<i>n</i> = 20)	Overall (<i>n</i> = 241)	<i>p</i> value
Age (years)	80.9 ± 10.0	81.0 ± 7.9	80.9 ± 6.3	80.9 ± 9.0	0.68
Male sex, <i>n</i> (%)	63 (47.4)	53 (60.2)	12 (60)	128 (53.1)	0.14
BMI (kg/m ²)	26.6 ± 7.4	28.2 ± 5.9	28.1 ± 5.3	27.3 ± 6.8	0.053
Atrial fibrillation or flutter, <i>n</i> (%)	31 (23.3)	72 (81.8)	14 (70)	117 (48.5)	< 0.001
Prior DVT/PE, <i>n</i> (%)	9 (6.8)	11 (12.5)	2 (10)	22 (9.1)	0.35
CHA2DS2-VASc score	5.2 ± 1.3	5.5 ± 1.2	5.7 ± 1.1	5.4 ± 1.3	0.10
ATRIA score	2.7 ± 1.0	2.7 ± 0.8	3.1 ± 0.8	2.7 ± 0.9	0.20
Indication for OAC, <i>n</i> (%)	40 (30.1)	76 (86.4)	16 (80)	132 (54.8)	< 0.001
Prior GI bleeding, <i>n</i> (%)	23 (17.3)	9 (10.2)	4 (20)	36 (14.9)	0.28
Dyslipidemia, <i>n</i> (%)	105 (78.9)	72 (81.8)	20 (100)	197 (81.7)	0.076
Hypertension, <i>n</i> (%)	117 (88)	81 (92)	20 (100)	218 (90.5)	0.19
Diabetes mellitus, <i>n</i> (%)	52 (39.1)	37 (42)	7 (35)	96 (39.8)	0.82
Prior PCI, <i>n</i> (%)	37 (27.8)	25 (28.4)	9 (45)	71 (29.5)	0.28
Peripheral arterial disease, <i>n</i> (%)	30 (22.6)	19 (21.6)	6 (30)	55 (22.8)	0.72
Cerebrovascular disease, <i>n</i> (%)	14 (10.5)	16 (18.2)	4 (20)	34 (14.1)	0.20
Chronic lung disease, <i>n</i> (%)	49 (36.8)	41 (46.6)	8 (40)	98 (40.7)	0.35
On hemodialysis, <i>n</i> (%)	5 (3.8)	2 (2.3)	1 (5)	8 (3.3)	0.76
NYHA class, <i>n</i> (%)					0.86
I	0 (0)	1 (1.2)	0 (0)	1 (0.4)	
II	7 (5.7)	5 (5.9)	2 (10.5)	14 (6.2)	
III	82 (66.7)	55 (64.7)	11 (57.9)	148 (65.2)	
IV	34 (27.6)	24 (28.2)	6 (31.6)	64 (28.2)	
LVEF (%)	52.9 ± 15.0	54.4 ± 14.2	55.3 ± 16.8	53.7 ± 14.8	0.60
Aortic valve area (cm ²)	0.6 ± 0.2	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.2	0.65
Aortic valve mean gradient (mmHg)	47.0 ± 13.8	41.7 ± 12.3	43.1 ± 15.6	44.8 ± 13.6	0.045
Aortic valve peak velocity (m/s)	4.4 ± 0.6	4.2 ± 0.6	4.3 ± 0.8	4.3 ± 0.6	0.047
Low gradient AS ^a , <i>n</i> (%)	24 (18)	11 (12.5)	2 (10)	37 (15.4)	0.42
Moderate or severe MR, <i>n</i> (%)	47 (38.5)	33 (38.4)	7 (36.8)	87 (38.3)	0.99
Valve sheath access site <i>n</i> (%)					0.41
Transfemoral	93 (69.9)	56 (63.6)	13 (65)	162 (67.2)	
Transapical	15 (11.3)	20 (22.7)	4 (20)	39 (16.2)	
Transaortic	24 (18)	11 (12.5)	3 (15)	38 (15.8)	

Table 1 continued

	AP (<i>n</i> = 133)	SAC (<i>n</i> = 88)	TT (<i>n</i> = 20)	Overall (<i>n</i> = 241)	<i>p</i> value
Other	1 (0.8)	1 (1.1)	0 (0)	2 (0.8)	

Continuous variables are presented as mean \pm standard deviation

AP antiplatelet therapy, SAC single antiplatelet plus oral anticoagulant therapy, TT triple therapy, BMI body mass index, DVT deep venous thrombosis, PE pulmonary embolism, ATRIA anticoagulation and risk factors in atrial fibrillation, OAC oral anticoagulation, GI gastrointestinal, PCI percutaneous coronary intervention, NYHA New York Heart Association, LVEF left ventricular ejection fraction, AS aortic stenosis, MR mitral regurgitation

^a Defined as aortic valve mean gradient < 40 mmHg, left ventricular ejection fraction < 50%, and aortic valve area < 1 cm²

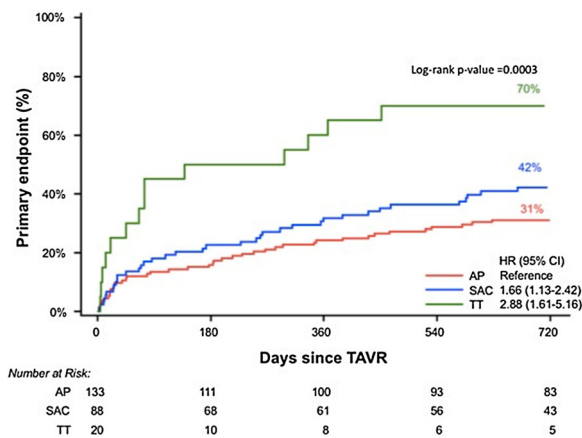


Fig. 1 Kaplan–Meier time-to-event curves for the primary composite endpoint of death, myocardial infarction, stroke, or major bleeding stratified by treatment group. TAVR transcatheter aortic valve replacement, HR hazard ratio, CI confidence interval, AP antiplatelet therapy, SAC single antiplatelet plus anticoagulant therapy, TT triple therapy

after TAVR, which is consistent with findings from other studies of patients undergoing TAVR [17, 18] and surgical aortic valve replacement [19]. We did not observe a benefit on ischemic endpoints with regimens using 2 or 3 antithrombotics compared to AP alone, as rates of MI and stroke were similar among the three treatment groups, but the study was not powered to do so. In addition to higher rates of bleeding with TT and SAC, we observed a higher mortality rate with these treatment strategies compared to AP. Importantly, our analysis shows that these effects persisted over a period of 2 years. However, while bleeding is reduced

when fewer antithrombotic agents are used, omitting an anticoagulant in patients with atrial fibrillation (or another indication for OAC) significantly increases the risk of thromboembolism, which often has more serious clinical consequences than bleeding.

The relatively low number of patients, especially in the TT group, is an important limitation of our study. Additionally, patients in the TT and SAC groups had higher rates of atrial fibrillation/flutter and an indication for OAC, which could have led to confounding by indication despite our use bootstrap resampling. Patients were categorized based on antithrombotic regimen at the latest time of follow-up, and results could differ if an intention-to-treat analysis was carried out. The patients we studied represent a high-risk cohort, as evidenced by the large burden of co-morbidities and high 2-year mortality rate. Thus, our results may not be applicable to lower-risk patients. Lastly, our study is observational in nature, and randomized trials are needed to determine the optimal antithrombotic regimen after TAVR in patients with and without an indication for anticoagulation. The recently reported aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation (ARTE) trial demonstrated that aspirin monotherapy reduced risk of bleeding, without increasing the risk of MI or stroke, compared to DAPT in TAVR patients [20]. Ongoing trials include ATLANTIS (NCT02664649), AUREA (NCT01642134), AVATAR (NCT02735902), ENVISAGE-TAVR (NCT02943785), GALILEO (NCT02556203), POPular-TAVI (NCT02247128), and TICTAVR (NCT02817789). The results of these trials will

likely inform future guidelines and clinical decision-making.

CONCLUSIONS

In a consecutive series of patients from our institution undergoing TAVR between 2009 and 2014, treatment with triple therapy or a single antiplatelet agent plus an oral anticoagulant was associated with an increased risk of the composite of death, MI, stroke, or major bleeding at 2 years compared to treatment with antiplatelet therapy alone, even after multi-variable adjustment. Further prospective investigations to determine the optimal antithrombotic regimen in TAVR patients are awaited.

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Compliance with Ethics Guidelines. All procedures performed in this study were in accordance with the ethical standards of the Institutional Review Board of Partners Healthcare in Boston, Massachusetts and with the

1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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